Greater Severity of Peanut Challenge Reactions Using a High fat versus Low Fat Matrix Vehicle

Pettersson, M Eleonore; Koppelman, Gerard H; Schins, Afke M M; van Ginkel, C Doriene; Flokstra-de Blok, Bertine M J; Kollen, Boudewijn J; Dubois, Anthony E J

Published in:
Clinical and Experimental Allergy

DOI:
10.1111/cea.13210

Received: 29 January 2018 | Revised: 11 April 2018 | Accepted: 10 May 2018

DOI: 10.1111/cea.13210

RESEARCH LETTER

WILEY

Greater severity of peanut challenge reactions using a high-fat vs low-fat matrix vehicle

Maris E. Pettersson[1,2] | Gerard H. Koppelman[1,2] | Afke M. M. Schins[1,2] | Cornella D. van Ginkel[1,2] | Bertine M. J. Flokstra-de Blok[2,3] | Boudewijn J. Kollen[3] | Anthony E. J. Dubois[1,2]

[1]Department of Pediatric Pulmonology and Pediatric Allergy, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands
[2]GRIAC Research Institute, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands
[3]Department of General Practice, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands

Correspondence
M. Eleonore Pettersson, Department of Pediatric Pulmonology and Pediatric Allergology, Beatrix Children's Hospital, University Medical Center Groningen, PO Box 30.001, 9700 RB, Groningen, The Netherlands.
Email: m.e.pettersson@umcg.nl

To the Editor,

Food allergy is a potentially life-threatening disease with a detrimental effect on the quality of life of caregivers and children.[1] Although many different types of food have been identified as potential elicitors of allergic reactions, only a small number of these foods cause the majority of reactions.[2]

Food consists of a complex mixture of nutrient and non-nutrient components and their molecular interactions, which are known as the food matrix. Individual matrix components, or the matrix as a whole, may interact with a food allergen and may influence the clinical response to that allergen.[3] However, data on this role of the food matrix in the clinical allergic response are scarce.

Establishing the influence of the food matrix is important because allergens are not ingested in a pure state. The main influences of the food matrix on an allergic reaction are considered to be caused by changes in allergen bioavailability and release, digestibility, and consequent interactions with the immune system.[3] The fat content of the food matrix has previously been shown to have an impact on this bioavailability of the allergenic protein in vitro for peanuts.[4] Thus, the food matrix could influence the uptake of allergens from food, and as a consequence confound the relationship between exposure to these allergens and the resultant clinical reaction.

A case series of double-blind, placebo-controlled food challenges (DBPCFC) with four peanut allergic patients by Grimshaw et al, suggested that a lower fat content of the peanut matrix reduced the amount of peanut required to elicit a reaction in three of the four subjects. These three subjects also had more severe symptoms in the food challenge using a high-fat peanut matrix.[5] However, due to the small number of subjects, only a descriptive evaluation of the results was possible and thus no definite conclusions could be drawn from this study.

So far, the current evidence suggests that the qualities of the food matrix may play an important role in the severity of the allergic reaction. However, to the best of the authors' knowledge, no previous study has shown an association between the fat content of a matrix and the clinical allergic response. A previous study from our centre with hen's egg challenges failed to find such an association.[6] The aim of this study was to examine possible matrix effects of a high- and low-fat content food matrix during DBPCFCs with peanut by comparing the severity and eliciting doses (EDs) of challenge reactions.

All positive diagnostic peanut DBPCFCs performed at the Beatrix's Children's Hospital in the University Medical Center Groningen between 2002 and 2014 were included. Food challenges were excluded if they were performed with any other than the two most frequently used recipes (*11 cases excluded*). In children with repeated DBPCFCs, only the first test was included (*37 cases excluded*). Fourteen cases were excluded because the challenge recipe was not specified.

DBPCFCs were performed as part of routine clinical care and according to previously published protocols.[7,8] The recipes used were peanut in cookies and peanut in gingerbread, with a fat content of 23.9% and 5.9%, respectively. The contents of the recipes are shown in Table 1. The dosing scheme for the two recipes was

TABLE 1 The contents of the peanut recipes used during DBPCFCs

	Peanut in gingerbread		Peanut in cookie	
Oven cooking temperature and time	160°C, 22 min		170°C, 25 min	
Fat content	5.9%		23.9%	
Ingredients	Self-rising wheat flour	40 g	Cane sugar	25 g
	Rice milk	35 g	Dairy-free margarine	20 g
	Caster sugar	29 g	Whole wheat flour	14 g
	Peanut flour (defatted)	8 g	All-purpose wheat flour	14 g
	Dairy-free margarine	5 g	Coconut	10 g
	Cinnamon, coriander, nutmeg, cloves, ginger, cardamom		Wheat germs	5 g
			Peanut flour (defatted)	2 g
Total		117 g		90 g

identical. The recipe used in the DBPCFC was based on the patient's own preference. The food challenge was deemed positive when objective and/or repeated subjective allergic symptoms were observed on the active day.

The severity of reactions during the DBPCFC was determined by scoring the symptoms according to van der Zee et al,[9] with a severity index ranging from 0 to 12. A second scoring system, published by Astier et al[10] was used for sensitivity analysis.

The influence of the matrix on the severity of the challenge reaction and ED was analysed by linear regression analysis, with correction for possible confounders. A variable was considered a confounder when it changed the beta coefficient by more than 10%. The alpha significance level was set at 0.05. The level of sIgE, ED, and reaction time during the DBPCFC was logarithmically transformed to normalize the residuals.

Two hundred and ten peanut allergic children were included in the analysis. Of these patients, 69 children ingested peanut in gingerbread, and 141 children ingested peanut in cookie during the active day of the DBPCFC. The included children were predominately boys (57.6%) and had a median age of 7.4 years with an interquartile range of 5.2-12.0 years. A substantial proportion of the children suffered from additional atopic disease. The median level of peanut specific IgE was 15.4 kU/L with an interquartile range of 3.9-60.8 kU/L. For further demographics according to the recipe used, see Table 2.

All assumptions of the linear regression analysis were met when using the scoring system by van der Zee et al However, when using the scoring system by Astier et al, the assumption of normally distributed residuals was not fulfilled. Thus, the final analysis was performed using the scoring system by van der Zee et al only.

Linear regression analysis showed that children challenged with the high-fat recipe, peanut in cookies, had more severe reactions during the DBPCFC (*B* = 0.77, 95%CI: 0.06-1.49, *P*-value= 0.03), compared to children challenged with the low-fat recipe, peanut in

TABLE 2 Differences in demographics and reaction parameters according to the recipe used analysed by linear or logistic regression

	Recipe used		*P*-value	B or Exp. B	95% CI
n = 210	Peanut in gingerbread (5.9% fat) n = 69	Peanut in cookie (23.9% fat) n = 141			
Age, y, median (IQR)	8.4 (5.2-12.8)	7.3 (5.3-11.9)	0.45	−0.46	−1.68-0.75
Gender, n (%)	Male: 37 (53.6) Female: 32 (46.4)	Male: 84 (59.6) Female: 57 (40.4)	0.41	1.28	0.71-2.28
Asthma, n (%)	35.0 (50.7)	98.0 (69.5)	0.01	0.44	0.24-0.81
Atopic dermatitis, n (%)	62.0 (89.9)	128.0 (90.8)	0.93	1.05	0.38-2.90
Allergic rhinoconjunctivitis, n (%)	32.0 (46.4)	71.0 (50.4)	0.59	0.85	0.48-1.52
Level of peanut sIgE, kU/L, median (IQR)*	13.6 (5.1-43.2)	15.6 (3.2-89.3)	0.73	0.07	−0.34-0.49
Eliciting dose, mg protein, median (IQR)*	70.0 (3.5-350.0)	70.0 (14.0-350.0)	0.45	0.22	−0.35-0.79
Reaction time DBPCFC, min, median (IQR)*	15.0 (5.5-40.0)	15.0 (5.0-42.0)	0.97	0.01	−0.33-0.35
Severity of DBPCFC reaction, score, median (IQR)	3.0 (3.0-5.0)	4.0 (3.0-6.0)	0.03	0.77	0.06-1.49
Severity of accidental reaction by history, score median (IQR)	2.0 (0.5-4.0)	2.0 (0.0-6.0)	0.44	0.35	−0.54-1.23

The high-fat recipe was used as reference. All these demographics were investigated as possible confounders for the relationship between the recipe and the severity of the challenge reaction and ED (for details, see statistical paragraph) logarithmically transformed.

gingerbread. However, there was no significant difference in the ED for the high- and low-fat recipes (B = 0.22, 95%CI: *–0.35-0.79*, P-value= 0.45). No confounders were identified in these relationships, including asthma.

The results of this study show that children receiving peanut in a high-fat matrix during an oral food challenge have more severe reactions compared to children undergoing this test with a low-fat matrix. This supports the role of the food matrix as a factor which may enhance the severity of both diagnostic challenge reactions as well as accidental reactions.

Our results showed no statistically significant difference in eliciting dose between the high- and low-fat recipes. This is at variance for what could be expected for foods with a high-fat content,[11] and reasons for this difference are not known. It should be noted, however, that reaction severity and eliciting dose are not closely related,,[12] so that changes in one need not be accompanied by changes in the other.

In a previous study by Libbers et al,[6] no matrix effect was shown for two different matrices used during DBPCFC with hen's egg. This suggests that matrix effects differ per type of allergenic food. Libbers et al suggested a possible explanation for differences in matrix effect between peanut and hen's egg to be the fat content of the allergenic food itself. Thus, the inherent difference in fat content between peanut and hen's egg may influence to what extent components of the allergenic food may dissolve in the food matrix in question and may therefore affect the rate of allergen release and bioavailability to the immune system.[6]

A limitation of this study is that patients were not randomized to the two recipes. The included children were allowed to choose which one of the two recipes they preferred, as recipe diversity is important to increase test compliance and avoid undue selection bias. Although a prospective, randomized study would be methodologically superior, it would be difficult, time-consuming and expensive to perform, and could result in a highly selected population of children willing and able to eat either recipe.

Another limitation of this study is that the two recipes used differed in other ways than the fat content. Moreover, the low-fat recipe had a higher concentration of peanut per gram of food matrix. However, it was the children receiving the high-fat matrix (with a lower peanut allergen concentration) that experienced more severe reactions, and thus, this does not seem to explain our results. Differences in the cooking time and temperature may also have accounted for differences in the resultant reactions, although these differences were small (see Table 1). Finally, some of the symptoms may have been caused by the higher fat content itself rather than a matrix effect on peanut. As such symptoms are mild, they would skew the data to showing milder reactions in the high-fat matrix group, which is contrary to what we observed. Thus, it is unlikely that such symptoms may account for the differences reported here.

In conclusion, this study shows a matrix effect for peanut, seen in differences in the severity of reactions in oral food challenges. Consequently, to be able to compare the results of oral food challenges in different patient groups or from different centres, the development of standardized food challenge materials may be necessary. Moreover, matrix effects could possibly influence accidental reactions to peanut and adverse events during peanut immunotherapy. This may be important from a regulatory perspective as well as for the food industry.

CONFLICTS OF INTEREST

None.

AUTHOR CONTRIBUTION

All authors fulfil the ICMJE authorship criteria.

ORCID

Maris E. Pettersson http://orcid.org/0000-0002-9005-3143
Cornella D. van Ginkel http://orcid.org/0000-0002-5247-2697

REFERENCES

1. Goossens NJ, Flokstra-de Blok BM, van der Meulen GN, et al. Food allergy knowledge of parents - is ignorance bliss? *Pediatr Allergy Immunol*. 2013;24:567-573.
2. NIAID-Sponsored Expert Panel, Boyce JA, Assa'ad A, et al. Guidelines for the diagnosis and management of food allergy in the United States: report of the NIAID-sponsored expert panel. *J Allergy Clin Immunol*. 2010;126:S1-S58.
3. McClain S, Bowman C, Fernández-Rivas M, Ladics GS, Ree RV. Allergic sensitization: food- and protein-related factors. Clin Transl. *Allergy*. 2014;4:11.
4. van Odijk J, Ahlstedt S, Bengtsson U, Borres MP, Hulthén L. Double-blind placebo-controlled challenges for peanut allergy the efficiency of blinding procedures and the allergenic activity of peanut availability in the recipes. *Allergy*. 2005;60:602-605.
5. Grimshaw KE, King RM, Nordlee JA, Hefle SL, Warner JO, Hourihane JO. Presentation of allergen in different food preparations affects the nature of the allergic reaction–a case series. *Clin Exp Allergy*. 2003;33:1581-1585.
6. Libbers L, Flokstra-de Blok BM, Vlieg-Boerstra BJ, et al. No matrix effect in double-blind, placebo-controlled egg challenges in egg allergic children. *Clin Exp Allergy*. 2013;43:1067-1070.
7. Vlieg-Boerstra BJ, Bijleveld CM, van der Heide S, et al. Development and validation of challenge materials for double-blind, placebo-controlled food challenges in children. *J Allergy Clin Immunol*. 2004;113:341-346.
8. Bindslev-Jensen C, Ballmer-Weber BK, Bengtsson U, et al. Standardization of food challenges in patients with immediate reactions to foods–position paper from the European Academy of Allergology and Clinical Immunology. *Allergy*. 2004;59:690-697.
9. van der Zee T, Dubois A, Kerkhof M, van der Heide S, Vlieg-Boerstra B. The eliciting dose of peanut in double-blind, placebo-controlled food challenges decreases with increasing age and specific IgE level in children and young adults. *J Allergy Clin Immunol*. 2011;128:1031-1036.
10. Astier C, Morisset M, Roitel O, et al. Predictive value of skin prick tests using recombinant allergens for diagnosis of peanut allergy. *J Allergy Clin Immunol*. 2006;118:250-256.

11. Mackie A, Knulst A, Le TM, et al. High fat food increases gastric residence and thus thresholds for objective symptoms in allergic patients. *Mol Nutr Food Res*. 2012;56(11):1708-1714. Epub 2012 Sep 19.
12. Pettersson ME, Koppelman GH, Flokstra-de Blok BMJ, Kollen BJ, Dubois AEJ. Prediction of the severity of allergic reactions to foods. *Allergy* 2018;73:1532-1540.

How to cite this article: Pettersson ME, Koppelman GH, Schins AMM, et al. Greater severity of peanut challenge reactions using a high-fat vs low-fat matrix vehicle. *Clin Exp Allergy*. 2018;48:1364–1367. https://doi.org/10.1111/cea.13210